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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/705,459	11/12/2003	Eilon Barnea	26884	8318

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	PAPER NUMBER
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/705,459	BARNEA ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-71* is/are pending in the application.

4a) Of the above claim(s) *1-36, 40-42, 50-71* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-39 and 43-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 November 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/18/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The present application was filed containing a power of attorney to Sol Sheinbein, D'vorah Graeser, Rochel Aboudi and Martin Moynihan. A correspondence address was supplied for G.E. Ehrlich (1995) Ltd c/o Mr. Anthony Castorina. No address was supplied for Sol Sheinbein, D'vorah Graeser, Rochel Aboudi and Martin Moynihan except through G.E. Ehrlich c/o Mr. Castorina.

Mr. Sol Sheinbein was excluded from practice before the Patent and Trademark Office (Office). The Office does not communicate with attorneys or agents who have been suspended or excluded from practice.

As a correspondence address, other than to G. E. Ehrlich c/o Mr. Anthony Castorina, is not of record, this Office action is being mailed to the other practitioners of record at his/her last known address as listed on the register of patent attorneys and agents. To ensure that a copy of this Office action is received in a timely manner to allow for a timely reply, a copy of the Office action is being mailed directly to the address of the inventor first named in the declaration or oath. Any reply by Applicant(s) should be by way of the remaining practitioner(s) of record and should include a new correspondence address.

2. Applicant's response filed 11/29/06 is acknowledged and has been entered.

3. The STIC branch of USPTO corrected the following errors in Applicant's CRF filed 11/12/03: "deleted invalid beginning/end-of-file text."

4. Applicant's election of one of the Inventions encompassed by Group XIV drawn to a peptide and composition thereof (claims 37-49 and 50-71) that is SEQ ID NO: 20 (claims 37-39 and 43-49) in Applicant's response filed 11/29/06 is acknowledged.

Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

Accordingly, claims 40-42 and 51-71 (non-elected Inventions encompassed by Group XIV) and claims 1-36 and 50 (non-elected Groups I-XIII) are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 37-39 and 43-49 are presently being examined.

5. The disclosure is objected to because of the following informalities:

a. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 27 at line 18 and on page 51 at line 22. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP 608.01.

b. The use of the trademark SEPHAROSE has been noted in this application, for example on page 50 at line 21. It should be capitalized wherever it appears and be accompanied by the generic terminology.
Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

c. The status of the priority application serial no. 09/865,548 should be updated in the first line of the specification, *i.e.,* "now US Patent No. 6,867,283.

d. There is a black bar on page 88 at line 1.

6. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(4) because reference characters "SEQ ID NO: 19" and "SEQ ID NO: 20" have both been used to designate the peptide GVYDGEEHSV, *i.e,* Figure 5D lists the MAGE-B2 peptide GVYDGEEHSV as SEQ ID NO: 19, whereas it is listed in the specification and sequence listing as SEQ ID NO: 20. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Appropriate correction(s) is/are required.

7. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the Examiner on form PTO-892, they have not been considered.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 37-39 and 43-49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to make and/or use the instant invention, a peptide that is SEQ ID NO: 20, a pharmaceutical composition comprising SEQ ID NO: 20 and a pharmaceutically acceptable carrier, including wherein SEQ ID NO: 20 is presented in context of an antigen presenting cell, or SEQ ID NO: 20 that comprises at least one modification rending it more immunogenic, including the modifications recited in instant claims 45 and 47.

The specification has not enabled the breadth of the claimed invention because the claims encompass: a peptide that is SEQ ID NO: 20 or a modified peptide variant thereof of the type recited in instant claims 45 and 47, or a pharmaceutical composition comprising SEQ ID NO: 20, a peptide that may not be immunogenic *in vitro* or *in vivo*, including in the latter instance for treatment. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the recited peptide can produce a therapeutic endpoint. The specification discloses no working examples with regards to the *in vivo* administration of the said peptide as a pharmaceutical composition, nor that the peptide is immunogenic or could be modified to render it more immunogenic, including by means of the modifications recited in instant claim 47, nor that the peptide is capable of stimulating CTL *in vitro*. The disclosed use of the peptide or of a pharmaceutical composition comprising SEQ ID NO: 20 is to treat cancer, either by *in vitro* stimulation of CTL for adoptive therapy or *in vivo* administration, respectively (page 27 at lines 4-6, Tables 8 and 9, page 114 at lines 19-30).

The specification discloses that peptide SEQ ID NO: 20 was detected on ovarian cancer cell line UCI-107, that it is a subsequence of testis-cancer antigen MAGE-B2 tumor-associated antigen and that a synthetic version of the said peptide can reconstitute HLA-A2 on the surface of RMA-S-HHD cells ([1276] and [0050]). The specification does not disclose that SEQ ID NO: 20 is capable of stimulating CTL *in vitro* or of inducing an immune response *in vivo*. The specification discloses that "Once tumor specific MHC bound peptides are identified and their ability to stimulate an immune response is demonstrated, such peptides become candidates for adoptive immunotherapy... The potential usefulness of identified immunogenic peptides should be evaluated by the presence of specific T cells directed against them in patients inflicted with the particular cancer using standard assays such as ELISPOT and CTL.

The assay of immunizing mice with the peptides described herein was meant to serve first as validation that these peptides are indeed MHC bound peptides with affinity for the HLA-A2.1 and as the preliminary indication of their immunogenic potential" (page 114 at lines 19-30).

Evidentiary reference Chaux *et al* (J. Immunol. 1999, 163: 2928-2936) teach varying results between peptides used *in vivo* in different clinical trials, injection of a HLA-A1 binding MAGE-A3 peptide correlated with tumor regression in about one third of patients, dendritic cells loaded with to other HLA-A1 binding peptides yielded only a partial response in one patient, and dendritic cells pulsed with two other HLA-A2 binding peptides produced no tumor regression. Chaux *et al* teach that it is necessary to monitor CTL responses of patients to provide information on the immunogenicity of various MAGE-A1 peptide, and that the immunogenicity of the peptides may vary in different individuals (especially Discussion section).

Evidentiary reference Marchand *et al* (Int. J. Cancer 80: 219-230, 1999) teach "Considerable further progress is needed, however, before immunization with tumor-specific antigens recognized by T cells becomes an effective and generally applicable cancer therapy" (second to last sentence of article).

Evidentiary reference Bodey *et al* (Anticancer Research 20: 2665-2676, 2000) teach "while cancer vaccine trials have yielded tantalizing results, active immunotherapy has not yet become an established modality of anticancer therapy (page 2665 at column 2). Bodey *et al* further teach "the use of active specific immunotherapy for cancer is still in its infancy despite several decades of clinical and basic research" (page 2668 at column 2).

Evidentiary reference Gao *et al* (J. Immunother. 23: 643-653, 2000) found that although anti-tumor CTL response was enhanced by immunization, the tumors failed to regress due to an association with lack of CTL migration to the tumor sites (abstract). Thus, Gao *et al* teach that activation of peptide epitope-specific CTL is not an appropriate endpoint, and an estimation of efficacy based upon this factor is not predictive of actual efficacy of treatment *in vivo*.

Evidentiary reference Marchand *et al* (Exp. Opin. Biol. Ther. 1(3): 497-510, 2001) teach "It is fair to say that in patients vaccinated with defined antigen, the immune responses induced have been so far very poor, if present. In some studies, immune responses were reported for some patients but without any correlation with the clinical responses. In addition, some patients with complete and long-term regressions of several melanoma metastases failed to mount a detectable response against the antigen present in the vaccine" (last paragraph at column 2 on page 505).

Evidentiary reference Berger *et al* (Int. J. Cancer. 111: 229-237, 2004) teach "Since strong CTL responses as observed in this patient are the goal of cancer vaccination but are so far only rarely observed, the thorough analysis of patients exhibiting either exceptional clinical and/or immunologic response appears critical to understanding how vaccine therapies work and can be further improved." (abstract). Berger *et al* further teach "immune therapy for tumor patients aims at harnessing the immune system to fight cancer. Indeed, clinical trials have already shown that tumor-specific T cells can be induced even in advanced cancer patients. The induction of tumor-specific T cells, however, is not necessarily associated with a clinical response. A major obstacle in evaluating the success of a cell-based immunotherapy lies in the fact that systemic immune responses detected in the blood may not reflect the actual situation in the tumor." (column 1, page 229). Berger *et al* teach "...tumor-reactive T-cell clones persisted for prolonged time in circulation but failed to infiltrate the analyzed tumor lesions. A possible explanation for this discrepancy is provided by the recent report from a transgenic mouse model that tumors may develop an intrinisic resistance to leukocyte infiltration and effector function that prevents even persistently high levels of activated tumor-specific T lymphocytes from eradicating the tumor" (paragraph spanning columns 1-2 on page 236).

Evidentiary reference Celis (J. Clin. Invest. 2002, 110(12: 1765-1768) teaches that "Unfortunately, the advantages that peptide vaccines have to offer are to some extent diminished by their inherent lack of immunogenicity, which so far has been reflected by their not-so-spectacular results in the clinic. Because the immune system in most species has evolved through time to fight life threatening infectious agents (and perhaps tumors), it should not be surprising that vaccines consisting of aseptic, endotoxin-free peptides are likely to be ignored and will likely be ineffective at inducing T cell immunity. In addition, peptides that are injected in aqueous solutions will be unsuccessful at stimulating CTL responses, either because of their rapid biodegradation (e.g., by proteases) or, worse, because of the induction of T cell tolerance/anergy, which results from the antigenic stimulation of CTLs by non-professional APCs." Celis further teaches that an additional complication resulting from the use of synthetic peptide-derived vaccines is the induction of low affinity CTLs, that while capable of killing target cells that are exogenously pulsed with peptide, are not able to recognize the target cells that naturally process and present the peptide epitope, such as malignant cells. These low quality CTLs would have little effect in fighting and controlling disease (especially page 1765 through the paragraph spanning pages 1765-1766.

Thus, even ***if*** there were factual evidence that patients with ovarian cancer or any other cancer or pathological condition could produce a peptide-specific immune response to the SEQ ID NO: 20 peptide, there is no factual evidence that the patient's condition would clinically improve, *i.e.,* be 'treated'. Based upon the teachings of the evidentiary references cited herein, it is evident that eliciting an immune response is not sufficient to evoke a clinically significant or specific anti-tumor effect.

Since SEQ ID NO: 20 has not been demonstrated to be immunogenic, it is unpredictable whether at least one modification such as recited in claims 46 and 47 could render the peptide more immunogenic and be used for the disclosed purpose.

Therefore, because of the demonstrated unpredictability in the art of cancer immunotherapy, in the absence of sufficient exemplification and guidance, one skilled in the art cannot make and/or use the pharmaceutical composition comprising the peptide with a reasonable expectation of success. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 37-39, 43, 48 and 49 are directed to an invention not patentably distinct from claims 1-3 of commonly assigned US 6,867,283. Specifically, the claims of '283 are drawn to a peptide that is SEQ ID NO: 13 and pharmaceutical composition thereof, including wherein said pharmaceutical composition thereof further comprises an APC presenting the said peptide (the peptide belongs to a non-elected Invention encompassed by Group XIV), and the instant claims 37-39, 43, 48 and 49 are drawn to a peptide, pharmaceutical composition thereof and including an APC presenting said peptide, wherein the peptide can be SEQ ID NO: 13.

12. Claims 44-47 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,867,283 in view of WO 96/25434 A1.

Claims 44-47 are drawn to a modified peptide that renders peptides more stable or more immunogenic in the body, such as peptide bond modification or residue modification.

Claims 1-3 of '283 are drawn to a peptide that is SEQ ID NO: 13 and pharmaceutical composition thereof, including wherein said pharmaceutical composition thereof further comprises an APC presenting the said peptide.

The claims of '283 do not recite wherein the peptide is modified such as recited in the instant claims.

WO 96/25434 A1 teaches that tumor associated peptides that are useful therapeutically may be modified to resist peptidase degradation, such as for example, by substituting D-amino acid residues, making the peptide cyclic rather than linear, substituting amino acid residues with non-natural amino acid residues, modifying the N or C terminus of the peptide, modifying the peptide bond, or making peptoid derivatives (abstract, page 9 at the last paragraph through page 18).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the peptide recited in claims 1-3 of '283 as taught by WO 96/25434 A1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make the peptide recited in claims 1-3 of '283 resistant to protease degradation as taught by WO 96/25434 A1 because the peptide recited in claims 1-3 of '283 is therapeutically useful as are the peptides taught by WO 96/25434 A1.

13. The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned US 6,867,283, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

14. Claims 37 and 43 are objected to because of the following informalities: Claims 37 and 43 recite SEQ ID NO that belong to non-elected Groups. Appropriate correction is required.

15. SEQ ID NO: 20 appears to be free of the prior art.

16. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the specification.

17. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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February 16, 2007

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